REMARKS

Claims 25-38 and 50-68 are active in the present application. The claims have been amended to correct typographical errors.

Claims 67 and 68 find support on page 41. Support for the specific activity of N-acetylglucosamine-1-phosphodiester α-N-Acetylglucosaminidase is found on page 22, lines 13-13 and page 37, lines 21-22. The specification has been amended to update the status of the parent application. No new matter has been added by these amendments.

Prior to the present invention, "[t]he lysosomal targeting pathways have been studied extensively and the process by which lysosomal enzymes are synthesized and transported to the lysosome has been well described. Kornfeld, S. (1986). "Trafficking of lysosomal enzymes in normal and disease states." *Journal of Clinical Investigation* 77: 1-6 and Kornfeld, S. (1990). "Lysosomal enzyme targeting." *Biochem. Soc. Trans.* 18: 367-374." (Page 3, lines 3-7).

The specification also describes that "[a]lthough the lysosomal targeting pathway is known and the naturally occurring enzymes involved in the pathway have been partially studied, the enzymes responsible for adding M6P in the lysosomal targeting pathway are difficult to isolate and purify and are poorly understood." (Page 4, line 24 to page 5, line 3).

However, "[a]s a result of the inability to purify or synthesize lysosomal enzymes with the desired oligosaccharide structures, [the lysosomal] enzyme preparations are inefficiently targeted to affected cells and are of limited effectiveness in the treatment of these diseases. There exists, therefore, a need for enzymes that can be used in enzyme replacement therapy procedures, particularly highly phosphorylated enzymes that will be efficiently internalized by the cell and transported to the lysosome." (Page 6, lines 3-9).

On page 4, lines 10-23, the specification notes that two Bao et al publications (one of which is references AZ cited in the Official Action) and Kornfeld et al have described the

bovine phosphodiester α-GlcNAcase, however "the proprietary monoclonal antibodies required to isolate these proteins have not been made available to others and the protein sequences for the enzymes used in these preliminary studies have not been disclosed."

Therefore, prior to the present invention, there was no disclosure or teaching that directed and enabled one to obtain and isolate either the phosphodiester α-GlcNAcase or phosphodiester α-GlcNAcase, which modify the oligosaccharide structure of lysosomal glycoproteins, which in turn, enables the efficient delivery of lysosomal enzymes to the lysosome.

The present claims provide methods of modifying a lysosomal hydrolase with, for example, N-acetylglucosamine-1-phosphotransferase with a specific activity of at least 10^6 pmol/h/mg, e.g., see Claim 25 and modifying a lysosomal hydrolase with phosphodiester α-GlcNAcase with a specific activity of at least about 472,000 units/mg, e.g., see Claim 39.

In view of the amendments and remarks contained herein, favorable reconsideration and allowance of all claims is requested.

The issues addressed in the Office Action are addressed in turn below.

The rejections of Claims 25-32, 35-41, 47-58 and 63-66 under 35 U.S.C. §103(a) over Kornfeld (BW); or the combination of Kornfeld (AY-2 or AZ-2) or Cuozzo et al (AX) in view of Bao et al (AZ) are respectfully traversed.

Kornfeld (BW) describes the purification and characterization of the bovine α-N-Acetylglucosaminidase and NOT N-acetylglucosamine-1-phosphotransferase as asserted by the Office (page 4 of the Official Action). Kornfeld (BW) only discusses that lysosomal enzymes are modified with both enzymes (page 23203, col. 1-2) but provides no description obtain N-acetylglucosamine-1-phosphotransferase with the specific activity included in the present claims. Therefore, the rejection over Kornfeld (BW) as it applies to Claims 25-32,

35-37, 50-58 and 63-66 is untenable because each of those claims require the presence of N-acetylglucosamine-1-phosphotransferase with a specific activity, which is not described in Kornfeld (BW).

As the rejection applies to Claims 39-44 and 47-49, the rejection is untenable for the following reasons.

It is well-established law that in order for a reference to anticipate a claimed invention, the reference or references must provide an enabling disclosure sufficient to place the public in possession of the claimed invention.[1] Likewise, this analysis extends to obviousness, where a holding of obviousness cannot be sustained "unless there is some known or obvious way to make the thing or to carry out the process."[2]

It was not until the filing of the present application where the specific antibodies were disclosed and therefore enabled by deposition under the terms of the Budapest Treaty at the American Type Culture Collection as described on page 15, lines16 17 for the PT18 antibody and the paragraph bridging pages 21-22 for the UC1 antibody (see the Preliminary Amendment filed on September 16, 2002) of the present specification, that such public availability was provided. Therefore, notwithstanding what the prior art cited describes, the skilled artisan had no way to make the N-acetylglucosamine-1-phosphotransferase or phosphodiester α-GlcNAcase with the specific activities included in the present claims.

Thus, the core issue here is whether Kornfeld (BW) or the combination of Kornfeld (AY-2 or AZ-2) or Cuozzo et al (AX) in view of Bao et al (AZ) enable the methods as claimed.

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[1]See MPEP 2121.01 and *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968).

[2]See *In re Collins*, 462 F.2d 538, 174 USPQ 333 (CCPA 1972), citing *In re Hoeksema*, see *supra*.

Kornfeld (BW) describes the purification of bovine N-acetylglucosamine-1-phosphodiester α-N-Acetylglucosaminidase with high specific activity, e.g, 498,500 units mg (see Table III on page 23207) which was dependent on a specific monoclonal antibody—compare the specific activity of the enzyme in method I, Table I on page 23205 to the specific activity obtained when the purification used the antibody, Table III.

However, while the Kornfeld (BW) describes the identification of a hybridoma cell line producing the antibody required to purify the phosphodiester α-GlcNacase, the document does not provide an enabling description for repeating the protocol to obtain the antibody and therefore, place that antibody into the public's possession. In fact, as described in Kornfeld (BW) on page 23205, bottom of col. 2, the protocol used to identify the one antibody from a pool of millions of possible hybridoma cell lines required numerous steps and screenings. It is unlikely that one could successfully reproduce the protocol and, in fact, obtain the same antibody needed to purify the enzyme to such a high purity and specific activity. This is the very reason that the Patent Office imposes a deposit requirement for biological deposits on applications for patents (see 37 C.F.R. § 1.801-1.809 and MPEP, Chapter 2400): "When an invention relates to a new biological material, the material may not be reproducible even when detailed procedures and a complete taxonomic description are included in the specification." (*In re Lundak*, 227 USPQ 90, 93-94 (Fed. Cir. 1985)). See also MPEP § 2402 and *Ajinomoto Co. v Archer Daniels-Midland, Co.*, 56 USPQ2d 1332, 1337-1338: "The deposit of biological organisms for public availability satisfies the enablement requirement for materials that are not amenable to written description or that constitute unique biological materials which can not be duplicated."

Thus, using the Office's own criteria, and applicable law for when biological deposit is required to enable an invention, it is clear that the Kornfeld (BW) does not enable the

purification of the phosphodiester α-GlcNacase with a high specific activity, which is an element in the present claims.

Therefore, the present claims would not have been obvious in light of the Kornfeld (BW) publication and as such withdrawal of the rejection is requested.

In a similar manner, the claims would not have been obvious in view of the combination of Kornfeld (AY-2 or AZ-2) or Cuozzo et al (AX) in view of Bao et al (AZ) because the combination fails to enable the purification of the phosphotransferase enzyme with a specific activity which is an element in the present claims.

Certainly, Kornfeld (AY-2), Kornfeld (AZ-2) or Cuozzo (AX) do not provide any description or suggestion to enable one to obtain the N-acetylglucosamine-1-phosphotransferase or phosphodiester α-GlcNAcase enzymes to a high specific activity.

The Kornfeld (AY-2) or (AZ-2) documents are review articles, which provide an overview of the lysosomal targeting pathway In particular, these Kornfeld documents disclose the proposed mechanism of high mannose phosphorylation (see Figures 2 and 6 of Kornfeld (BZ) and Figure 1 of Kornfeld (BY)) and identify that partially purified protein preparations of N-acetylglycosaminylphosphotransferase and α-N-acetylglucosaminidase have been identified and are involved in the this phosphorylation activity (see page 1, col. 1, lines 1-20 of Kornfeld (BY)). It is also noted that these documents are described in the present specification on pages 2-5 (see above).

The Cuozzo et al (BX) disclosure provides a crude partially purified N-acetylglucosamine-1-phosphotransferase from rat liver (see page 14491, last paragraph, column 2). Using this crude preparation of enzyme, Cuozzo et al demonstrate the transfer of

[β-^{32}P]UDP-GlcNAc to cathepsin L (see page 14491, col. 2, last paragraph to page 14492, col. 1).

Bao et al (AZ-*J Biol Chem* 271(49):31446-31451 (1996)—"Bao II") characterize the enzyme purified in the companion paper Bao et al (*J Biol Chem* 271(49):31437-31445 (1996) a copy of which is attached for the Examiner's reference-"Bao I") and which is described in the present application on page 4, lines 10-14. Similarly, Bao II is described in the specification on page 4, lines 14-20. In these publications, the purification of bovine N-acetylglucosamine-1-phosphotransferase with high specific activity, e.g, at least 10^6 pmol/h/mg was dependent on a specific monoclonal antibody—compare the specific activity of the phosphotransferase in method I, Table I on page 31439 of Bao I to the specific activity obtained when the purification used the antibody, Table II on page 31441 of Bao I.

However, while Bao I describes the identification of a hybridoma cell line producing the antibody required to purify the phosphotransferase, the document does not provide an enabling description for repeating the protocol to obtain the antibody and therefore, place that antibody into the public's possession. In fact, as described in Bao I on page 31438, bottom of col. 2, the protocol used to identify the one antibody from a pool of millions of possible hybridoma cell lines required numerous steps and screenings. It is unlikely that one could successfully reproduce the protocol and, in fact, obtain the same antibody needed to purify the enzyme to such a high purity and specific activity. Thus, as discussed at length above concerning the Kornfeld (BW) rejection, it is clear that the combination of prior art does not enable the purification of the phosphotransferase with a high specific activity, which is an element in the present claims (see 37 C.F.R. § 1.801-1.809 and MPEP, Chapter 2400).

Therefore, Applicant requests that the rejection under 35 U.S.C. § 103 over the combination of Kornfeld (AY-2 or AZ-2) or Cuozzo et al (AX) in view of Bao et al (AZ) be withdrawn.

The rejection of 25-32, 35-44, 47-58 and 63-66 under the doctrine of obviousness-type double patenting over the parent application, U.S. Serial no. 09/635,872, now U.S. Patent 6,534,300 is addressed by the Terminal Disclaimer filed herewith.

The rejections under 35 U.S.C. § 112, first and second paragraphs are addressed by amendment.

Applicant submits that the present application is ready for allowance. Early notification of such allowance is requested.

Respectfully submitted,

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